Tissue Paclitaxel and Outcomes of Patients with Rutherford Class 5/6 Ischemia Treated with DCB Angioplasty

Rabih A. Chaer[1*], MD, Patrick Cherfan[1], MD, Adham N. Abou Ali[1], MD, Othman M. Abdul-Malak[1], MD, Sina Asaadi[1], MD, Mohammad H. Eslami[1], MD, Efthymios D. Avgerinos[1], MD, Karim M. Salem[1], MD, Georges Al-Khoury[1], MD, Michel S. Makaroun[1], MD, Maria E Romero[2], MD, Renu Virmani[2], MD

[1]Division of Vascular Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pa.

[2]CVPath Institute, Inc, Gaithersburg, Md.

*Corresponding Author:

Rabih A. Chaer, MD, MSc

200 Lothrop Street

Pittsburgh, Pa 15213

E-mail address: chaerra@upmc.edu

Study Title	**Evaluation of paclitaxel in patients with CLI (critical limb ischemia) and femoropopliteal occlusive disease treated with DCB (drug coated balloon) angioplasty**
Protocol Number	**PRO- PRO15120093**
Sponsor	**Funded by Department**
Study Design	**Prospective, single center, non-randomized, single arm clinical trial**
Study Objective	**To evaluate the paclitaxel level in debrided tissue following DCB (drug coated balloon) angioplasty for femoropopliteal occlusive disease in patients with CLI (critical limb ischemia) and tissue loss to see if it impacts wound healing**
Primary Study Endpoint	**Primary Study Endpoints:** **-wound healing rate** **-amputation free survival** **-amputation free and wound healing** **-primary sustained clinical improvement** **Major adverse events (MAE)** **-Death of any cause** **-Major amputation of target limb**
Secondary Study Endpoints	**Secondary Study Endpoints:** **-Primary patency at 1,3,6 and 12 months** **-secondary patency at 1,3,6 and 12 months** **-rate of sever >50% restenosis measured by duplex ultrasound** **-rate of reinterventions**
Subject Population	**Patients age 40 years to 95 years identified with CLI (critical limb ischemia) and tissue loss with a Rutherford category of 5 or 6**
Number of Subjects	**50**
Device to be Used **(FDA approved/commercially available)**	**Medtronic Admiral Balloon <u>OR</u>** **Bard Lutonix Balloon**
Expected Time to Complete Enrollment	**48 months**
Schedule of Events	**<u>Baseline/Procedure</u>**

	-Inclusion/exclusion criteria review **-Informed consent** **-medical history review** **-concomitant medication review** **-office visit** **-arterial Doppler (ABI/PVR/Toe pressures)** **-Rutherford Category** **-Angiogram** **-ballooning (Admiral or Lutonix)** **-stenting (if indicated)** **-wound debridement/toe amputation** **-histological analysis** **-pregnancy test (women of child-bearing age)** **1,3,and 6 month follow-up visits** **-concomitant medication review** **-office visit** **-arterial Doppler (ABI/PVR/Toe pressures)** **-wound debridement** **-histological analysis** **-AE assessment** **12 month visit** **-office visit** **-arterial Doppler (ABI/PVR/Toe pressures)** **-AE assessment** **-study exit**
Study Principal Investigator	**Rabih A. Chaer, MD**
Contact Information	**412-802-3333 or email chaerra@upmc.edu**

◦Background and Objective

The use of DCB in patients with CLI and tissue loss has recently raised some concerns after the IN PACT deep trial using paclitaxel coated balloon angioplasty in the tibial arteries was terminated. Paclitaxel (also known as Abraxane) is classified as an antineoplastic drug.

In this trial, there were stronger trends toward a higher rate of major amputation (8.8% vs 3.6%; P = .080) and a lower rate of major amputation-free survival (81.1% vs 89.2%; P = .057) in the DEB arm at 12 months, despite the presence of longer lesions and deeper wounds in the patients who underwent standard balloon angioplasty. Wound healing was similar in the 2 groups, but overall procedural complications were more common with the DEB (9.7% vs 3.4%; P = .035).

Our objective is to evaluate the paclitaxel level in debrided tissue following DCB (drug coated balloon) angioplasty for femoropopliteal occlusive disease in patients with CLI (critical limb ischemia) and tissue loss to see if it impacts wound healing.

◦Question

Although the association between the DCB therapy and limb outcomes could not be clearly linked to the use of antiproliferative agents, the findings of paclitaxel crystals downstream of the treated lesions, although in small amounts, has raised concerns about the safety of such therapy in patients with CLI and tissue loss.

These concerns, however, may not translate to patients with femoropopliteal occlusive disease as the amount of paclitaxel reaching the foot may be even smaller after being filtered by the calf musculature.

Since the use of DCB angioplasty in the SFA and popliteal has been shown to deliver significantly more durable outcomes compared to standard angioplasty alone, with reported primary patency rates of almost 90% at one year, this therapy may even be more needed in patients with tissue loss where prolonged patency is essential for wound healing.

We hypothesize that DCB angioplasty of femoropopliteal occlusive disease using a 4, 5 or 6mm diameter InPact balloon is safe and effective in patients with CLI and tissue loss with negligible paclitaxel levels in debrided wounds (Rutherford 5,6).

◦Patient Population

Inclusion criteria:

Ages Eligible for Study: 40 Years to 95 Years

Genders Eligible for Study: Both

Patient population: all patients with CLI and tissue loss scheduled for endovascular intervention for fem pop occlusive or multilevel disease.

Patient or patient's legal representative have been informed of the nature of the study, agrees to participate and has signed an Ethical Committee approved consent form

Patient has documented chronic Critical Limb Ischemia (CLI) in the target limb prior to the study procedure with Rutherford Category 5 or 6

General Angiographic Inclusion Criteria

Single or multiple lesions with ≥70% diameter stenosis (DS) of different lengths in the SFA and/or popliteal arteries.

Iliac inflow or Tibial outflow interventions can be done at the discretion of the investigator with standard balloon PTA

All subjects with CLI (critical limb ischemia) intended to be treated with a drug coated balloon

Exclusion criteria:

Patient unwilling or unlikely to comply with Follow-Up schedule

*Since paclitaxel can be harmful to an unborn child, participants (male and female) of childbearing age will be required to have a blood and/or urine test before participating in this study. A discussion related to Planned Parenthood will be held with participants of childbearing age. Any participant that is pregnant or believes that they might be pregnant will be withdrawn from the study immediately. At the completion of the study, the investigator will discuss with the participant when it might be safe to become pregnant or become a new father."

◦Proposed Study Design

Research design

50 patients with documented chronic Critical Limb Ischemia (CLI) in the target limb prior to the study procedure with Rutherford Category 5 or 6 will be enrolled and followed for at least one year.

Hemodynamic vascular lab testing with arterial Doppler (ABI, PVR, toe pressures) and arterial duplex imaging of the affected leg will be performed in an accredited vascular lab pre-enrollment as well as at 12 months post intervention.

Only patient with severe femoropopliteal occlusive disease (with or without multilevel disease including iliac inflow or tibial outflow disease) requiring intervention will be enrolled. The use of DCB angioplasty will be restricted to the fem pop segment. Patients with multilevel disease also requiring iliac inflow and/or tibial outflow intervention to establish in line flow to the foot will be treated with standard balloon angioplasty/stenting as per the standard of practice in the USA.

Procedures will be done in an operating room angiography suite, and patients with tissue loss will undergo concomitant wound debridement or planned toe amputation/debridement as per the standard of practice. The tissue obtained will be sent for histological analysis.

Wound care will be provided per standard of practice on a weekly or bi-weekly basis, and tissue obtained from further debridement/amputation done in the office setting or operating room will also be obtained from analysis.

From the obtained tissue specimen, the arterioles per each histologic section will be examined for any foreign material, paclitaxel crystals medial arterial wall inflammation, foreign-body reaction, emboli, and medial necrosis. Changes will be characterized as single or clusters of multiple small vessels (predominately arterioles) with varying degrees of eosinophilic fibrinoid necrosis, SMC apoptosis and loss, and adventitial inflammation or vasculitis consisting primarily of lymphocytes. The number of arterioles with findings will be expressed as a percentage of the total number of arterioles evaluated.

Treatment:

Patients that meet all of the inclusion and none of the exclusion criteria will be consented for the study. Each participant will receive angiogram with DCB (drug coated balloon)/stenting with wound debridement. Paclitaxel® coated balloons will be used for patients. For the study, 50% of the study population will receive the Bard Lutonix balloon. The other 50% will receive the Medtronic Admiral balloon. Both FDA approved devices contain the drug paclitaxel. Tissue samples will be sent to pathology for specific staining to evaluate trace evidence of the drug paclitaxel. Patients will be asked to return at 1 month, 3 months, 6 months and 12 months post procedure. If indicated, patients with tissue loss may have an in-office wound debridement. Tissue samples from these procedures will also be sent to pathology to evaluate for wound healing.

Primary Outcome Measures:

.Wound healing. Rate of Wound Healing [Time Frame: 12 months]

Percentage of participants with wound healing defined as > 50% area/volume reduction of baseline ulcer(s) in the treated leg at 1 year.

.Amputation Free Survival [Time Frame: 12 months]

Percentage of participants with a 1 year amputation free survival.

.Amputation Free Survival and Wound Healing [Time Frame: 12 months]

Percentage of participants with a 1 year amputation free survival and wound healing. Wound healing is defined as > 50% area/volume reduction of baseline ulcer(s) in the treated leg at a specified time point.

•MAE (Major Adverse Events) [Time Frame: 12 months]

Percentage of participants with a MAE (Major Adverse Events) at 1 year. Major Adverse Events, defined as Death of any Cause, Major Amputation of target limb.

Secondary Outcome Measures

.Primary patency at 12 months as measured by duplex ultrasound

◦Relevance to Drug Coated Balloon Therapies in Patients with CLT and Tissue Loss

The findings of this study will determine the tissue levels of paclitaxel in debrided tissue in patients with CLI, and establish the safety and efficacy of DCB for femoropopliteal occlusive disease in those patients. I will reinforce the use of both Medtronic's Admiral DCB and the Bard Lutonix DCB in this patient population by alleviating physician concern about increased limb loss secondary to Paclitaxel in patients with tissue loss.

Statistical Analysis

Data analysis was carried out using the Statistical Package for the Social Sciences, version 26 (IBM Corp, Armonk, NY) and all tests were two-sided with statistical significance defined at P0.05. Continuous variables were reported as mean ± SD, and categorical variables were reported as frequency (%). Chi-square tests were used to compare categorical variables between the study groups. Kaplan-Meier (KM) survival analysis was used to estimate stent primary patency and survival rates. Multivariate logistic regression analysis was used to determine factors associated with major adverse limb events (MALE); odds ratios (OR) and their corresponding 95% confidence intervals were reported as measures of associated factors.